Procter&Gamble
PHARMACEUTICALS

Mail: *The Procter & Gamble Company*
Health Care Research Center
P.O. Box 8006
Mason, Ohio 45040-8006

Shipping: *The Procter & Gamble Company*
Health Care Research Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

3 June 2002

Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket No. 02D-0095
Draft Guidance for Industry on Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications

Dear Sir or Madam:

Reference is made to the Draft Guidance for Industry on Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications. Submitted herewith, are comments from Procter & Gamble Pharmaceuticals regarding the draft guidance document. We appreciate the opportunity to respond to the Agency's request for comments.

Comments

Section IV. B. Using observed concentration versus concentration-controlled trials. One would agree that if everyone is administered the same dose, the ability to assess the influence of different covariates on the exposure /response relationships may be difficult due to confounding effects (e.g. renal impairment and higher concentrations). However, the discussion should also mention that if dosage adjustments are implemented into Phase 2/3 for appropriate subgroups, the ability to assess the influence of these subgroups (e.g. renal impairment) may be significantly improved.

Line 413 – Please clarify your use of "rigor" which is always required.

Lines 422/423. Randomization is critical at all stages, not just for those studies intended to support regulatory decisions.

Table I. Points to Consider in Study Design and Exposure-Response Study Analysis. Consider the addition of blinding as a point to consider for all studies, especially if it includes subjective assessment or assessors.

Section V.C.1.e. In addition to changes in plasma protein binding between various diseases states, time-dependent binding should also be mentioned since it may also complicate the analysis of exposure/response analysis.

Lines 514/521. AUC should be replaced by Cavg. It maintains consistency between the various types of exposure (all concentrations) used to assess relationships. More importantly, it allows one to appropriately analyze data from a study where the dosing interval is varied, in an attempt to reduce the

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correlation between the various measures of exposure. It is unclear how one would use AUCτ in the analysis when the dosing interval is varied without standardizing to the dosing interval (i.e., Cavg).

Thank you again for the opportunity to provide comments. If you have any questions regarding the above, please contact the undersigned by telephone at 513.622.5278, or by facsimile at 513.622.5363.

Sincerely,

Wendy Sauber

Wendy M. Sauber
Section Head, U.S. Regulatory Affairs

MICHAEL D SHILLEH
PROCTOR & GAMBLE HCRC
8700 MASON MONTGOMERY RD
MASON OH 45040
(513)622-1376

SHIP DATE: 03JUN02
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HFA-305
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